IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

**DECLARATION OF ARTHUR H. KIBBE, Ph.D.,
IN SUPPORT OF DEFENDANT IMPAX LABORATORIES, INC.'S
RESPONSIVE CLAIM CONSTRUCTION BRIEF**

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DECLARATION OF ARTHUR H. KIBBE, Ph.D., IN SUPPORT OF DEFENDANT IMPAX LABORATORIES, INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

I, Arthur H. Kibbe, Ph.D., declare:

1. I am a pharmaceutical formulations scientist with over 35 years of experience in the fields of biopharmaceutics, pharmacokinetics and pharmaceutical excipients. My qualifications are set forth in paragraphs one through seven of the Declaration of Arthur H. Kibbe, Ph.D., In Support of Defendant's Markman Brief (D.I. 165).

"Extended Release Formulation"

2. I do not dispute that the term "extended release formulation" has a plain and ordinary meaning to one of ordinary skill in the art. Indeed, Exhibit 2 to my Declaration in support of Impax's Opening Claim Construction Brief attached an excerpt from the very same Remington textbook to which Wyeth's expert refers. *Compare* Exhibit 2 to Declaration of Arthur H. Kibbe, Ph.D. in Support of

Defendant's Markman Brief (D.I. 165) *with* Exhibit B to Declaration of James W. McGinity, Ph.D. (Exhibit 5 to the Declaration of Karen Jacobs Louden in Support of Wyeth's Opening Markman Brief) (hereafter "McGinity Decl.").

3. However, it is my opinion that a person of ordinary skill in the art reading the patent would understand that the claims do not use the term "extended release formulation" in its ordinary sense. As I explained in my first declaration, this is because the specification states that the inventive formulation has specific ingredients, so the use of that term in the claims would necessarily imply to a person of ordinary skill in the art that the "extended release formulation" to which the claims refer consists of venlafaxine hydrochloride, microcrystalline cellulose (hereafter "MCC") and optionally hydroxypropylmethylcellulose (hereafter "HPMC")

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6. It is thus no surprise that the inventors believed that "the invention comprises an extended release formulation of venlafaxine hydrochloride . . . in spheroids comprised of venlafaxine hydrochloride, [MCC] and, optionally, [HPMC] coated with a mixture of ethyl cellulose and [HPMC]." '171 Patent, Abstract.

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Table 1 of the Patent Specification

8. Table 1 of the specification of the patents-in-suit sets forth a broad *in vitro* dissolution profile – the rate at which a pharmaceutical composition is released during a test in the laboratory.

9. Table 1 by itself says nothing about which ingredients might or might not be useful in achieving the stated dissolution profile. Table 1 does not teach anything about how to make a particular formulation that would achieve those *in vitro* dissolution rates. Table 1 contains the resulting dissolution profile that a

formulator would be trying to achieve; it does not tell how one would achieve those results.

10. Table 1 is described in the specification as providing "the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form." '171 Patent, 6:37-40. Furthermore, the title of Table 1 is "Acceptable Coated Spheroid Dissolution Rates." 6:52. One of ordinary skill in the art would understand Table 1 to be limited to coated spheroids to be used in capsule form. More specifically, one of ordinary skill in the art would understand Table 1 to be limited to "this invention in capsule form," specifically the MCC matrix formulation that I described in my first declaration (containing venlafaxine hydrochloride, MCC, and, optionally, HPMC) in capsule form.

11. In his declaration in support of Wyeth's opening claim construction brief, Dr. McGinity states that Table 1 applies to any potential extended release venlafaxine formulation:

> In addition, the patents teach one of ordinary skill in the art to use the *in vitro* dissolution information in the specification as a bench test to screen for extended release formulations of venlafaxine that would most likely meet the *in vivo* limitations of the claims, **regardless of how they are made**, further confirming that the "use aspect of the invention" is broadly disclosed and claimed in the patents-in-suit."

McGinity Decl. ¶ 31 (emphasis added). I understand Dr. McGinity to be referring to use of the *in vitro* dissolution profile in Table 1 as a screen for developing extended release venlafaxine formulations of all types, regardless of how they are made.

12. I disagree with Dr. McGinity's statement. Table 1, as described in the specification and in its title, does not apply to dosage forms beyond coated

spheroids, and does not apply beyond the coated spheroids of "this invention in capsule form", namely the disclosed formulation using venlafaxine hydrochloride, MCC, and, optionally, HPMC, in capsule form.

13. More generally, there are numerous methods for drug delivery, and Table 1 does not provide any guidance as to these other methods. For example, extended release methods such as a patch, a tablet, an implantable device, and an intramuscular injection could all provide a therapeutic blood plasma concentration of a drug, but each would have different *in vitro* properties. One of ordinary skill in the art would understand the patent to be focused on solid oral dosage forms, and have little applicability to other extended release delivery methods. Nor would one expect the *in vitro* dissolution profile of an oral capsule to be particularly useful or predictive for a suppository, even if they contained the same active ingredient. Table 1 simply does not provide guidance for extended release venlafaxine formulations across all these different dosage forms. Table 1 does not provide guidance for developing extended release venlafaxine formulations "regardless of how they are made," contrary to Dr. McGinity's statement.

14. In paragraph 18 of his declaration, Dr. McGinity states that the patents "provide guidance on how to modify formulations" which do not fit within the ranges set forth in Table 1 by filling capsules with a mixture of fully-coated and less-coated spheroids. This "guidance" teaches nothing to one of ordinary skill in the art, since this technique has been known in the art since the 1950s and is commonly taught in pharmacy schools. For example, the technique is described in U.S. Patent Number 2,738,303, issued March 13, 1956, attached as Exhibit 3 to this Declaration.

15. I note several places in Wyeth's Opening Brief, and Dr. McGinity's declaration, where they note that Table 1 provides a screen for the "likely" or "most likely" formulations that will provide *in vivo* therapeutic results. *See* Wyeth's Opening Brief at 6, McGinity Decl. ¶ 18, 31. Those statements are not completely predictive, i.e., they do not state that conformance with the *in vitro* dissolution profile of Table 1 *will* provide therapeutic results in all cases; they merely say it is "likely."

16. The *in vitro* dissolution profile of a pharmaceutical composition is not perfectly predictive of the *in vivo* properties of the composition. It is impossible to say with certainty that a drug matching a given *in vitro* dissolution profile will or will not provide therapy when given to a patient. Some compositions matching the *in vitro* dissolution profile of a therapeutically effective composition will not provide therapy. Likewise, some compositions not matching the *in vitro* dissolution profile of a therapeutically effective composition will provide therapy.

17. It is for this reason that the FDA requires pharmacokinetic studies before approving new formulations of all pharmaceuticals, even when the new formulation precisely matches the *in vitro* dissolution profile of a formulation that has already been approved.

18. When developing a generic version of an existing drug, it is accepted in the art that one should usually begin by ascertaining the *in vitro* dissolution profile of the existing drug, and then one should attempt to match that *in vitro* dissolution profile, since one's goal in developing a generic version is to reach bioequivalence. This process is known in the art as "reverse engineering," and is an accepted and legitimate formulation technique.

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21. I also note that it was known in the art since at least the early 1990s that once-a-day dosages of medications were generally desirable because of better patient compliance and reduced side effects.

The "Use Aspect of the Invention"

22. Dr. McGinity states that the "use aspect" of the invention encompasses "the use of any extended release formulation of venlafaxine hydrochloride, other than a hydrogel tablet, that provides for the claimed in vivo parameters." McGinity Decl. ¶ 34.

23. I do not understand the patents to disclose or teach any "use aspect" of the invention other than the use of the disclosed formulations that include venlafaxine hydrochloride, MCC, and, optionally, HPMC. As discussed above and in my first declaration, the patent specification does not teach or disclose any other formulation, nor is there any evidence the inventors were in possession of any other formulation that provided the requisite therapeutic results. The dissolution profile set forth in Table 1 is limited to the "coated spheroids" of

"this invention in capsule form." Table 1 provides no disclosure of other methods to "use" the invention, other than the use of the disclosed formulations of venlafaxine hydrochloride, MCC, and, optionally, HPMC.

"Troughs and Peaks"

24. I understand Wyeth and Impax to have different claim constructions for the phrase: "eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride."

25. One of ordinary skill in the art would understand the language "troughs and peaks of drug concentration in a patient's blood plasma attending the … plural daily doses of venlafaxine hydrochloride" to be referring to the blood plasma concentration associated with the "plural daily doses." In essence, the language refers to eliminating certain aspects (troughs and peaks) of the blood plasma concentration associated with plural daily dosing.

26. One of ordinary skill in the art would not understand the disputed claim language to be describing a particular extended release blood plasma curve. To the contrary, the disputed language says nothing about the extended release blood plasma curve. The claim language only discusses the profile of "plural daily doses," for instance, the profile of an immediate release formulation given twice a day. The claim states that it is a method for "eliminating the troughs and peaks . . . of plural daily doses." There are no words or terms in the disputed claim language that describe or refer to the extended release blood plasma concentration in any way.

27. I understand Wyeth's proposed construction of the disputed claim language is as follows: "A method in which the extended release formulation is

administered once in a 24-hour period, resulting in a venlafaxine blood plasma concentration that rises to a maximum value, followed by a generally protracted decrease over the remaining period while maintaining during that 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated, thereby eliminating the multiple sharp peaks and troughs resulting from multiple daily dosing of the same total daily dose of the immediate release formulation as reflected in a graph of venlafaxine blood plasma concentration versus time."

28. Wyeth's proposed construction for the disputed claim language contains a description of an extended release blood plasma concentration curve allegedly resulting from the invention. This proposed construction does not describe the disputed claim language which is clearly directed to the elimination of "troughs and peaks" of plural daily dosing.

29. In his declaration in support of Wyeth's Opening Claim Construction Brief, Dr. McGinity states that "[t]he 'use aspect' of the patented invention is described as eliminating the sharp peaks and troughs" in venlafaxine blood plasma levels associated with multiple daily dosing. McGinity Decl. ¶ 17 (emphasis added).

30. The terms "peak" and "trough" have a plain meaning to one of ordinary skill in the art. A "peak" blood plasma level is simply the highest level and a "trough" is simply the lowest level prior to the next dose during a standard dosage regimen. The plain meanings of "peak" and "trough" do not encompass any description of how quickly the blood plasma level rises to the peak or falls to the trough, i.e., the "sharpness" of the peaks and trough.

31. Dr. McGinity's statement concerning the "sharp peaks and troughs" is thus outside the plain meaning of the terms "peak" and "trough" which are the terms used in the claims.

32. I note that Wyeth's expert Dr. Sawchuk states that "Because the extended release formulation of venlafaxine hydrochloride is administered only once a day, only one peak and one trough in venlafaxine plasma concentration are observed over a twenty-four hour interval. This clearly differs from the plasma concentration-time profile of the immediate release product, dosed two or three times daily, which would result in two or three peak-troughs pairs in the twenty-four hour period, since each dosing interval during the day would exhibit its own peak and trough plasma concentration of drug." Declaration of Ronald J. Sawchuck, Ph.D. at 11-12. I agree with this statement, which comports with Impax's construction of the disputed claim language.

33. In contrast to how the patent repeatedly describes the "invention" as comprising venlafaxine hydrochloride, MCC, and, optionally, HPMC, the patent does not repeatedly describe a specific shape of the immediate release venlafaxine blood plasma concentration curve. The patent does not characterize "the method of this invention" as being explicitly limited to eliminating sharp peaks and troughs, nor does "the method of the invention" contain the other limitations that appear in Wyeth's construction.

34. As a general matter, reducing the number of doses given to a patient over a 24-hour period inherently reduces the number of peaks and troughs in blood plasma levels. When a patient receives a dose, the patient's blood plasma concentration of the active ingredient increases. Indeed, this increase is the very reason the dose was administered. Each such increase causes a peak. After each peak comes a trough, as the drug is eliminated or metabolized. The trough is the

lowest point the plasma concentration reaches prior to the next dose. Thus, a person of ordinary skill in the art would understand that there is one peak and one trough associated with every dose administered to the patient.

35. Accordingly, once-a-day dosing will cause one peak and one trough per day; twice-a-day dosing will cause two peaks and two troughs per day; and so on. Thus, every extended-release dosage form eliminates at least some peaks and troughs compared to an immediate-release counterpart, because extended-release dosage forms, by definition, are administered less frequently than immediate-release dosage forms.

DISSOLUTION OF WYETH AND IMPAX FORMULATIONS

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38. I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct and that this declaration was executed on this 25th day of May, 2007 at Wilkes-Barre, Pennsylvania.

Arthur H. Kibbe, Ph.D.

May 25, 2007

EXHIBIT 1

ENTIRE EXHIBIT UNDER SEAL

EXHIBIT 2

ENTIRE EXHIBIT UNDER SEAL

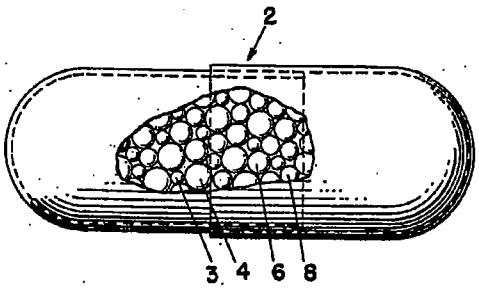
EXHIBIT 3

March 13, 1956 R. H. BLYTHE 2,738,303

SYMPATHOMIMETIC PREPARATION

Filed July 18, 1952

Fig. 1



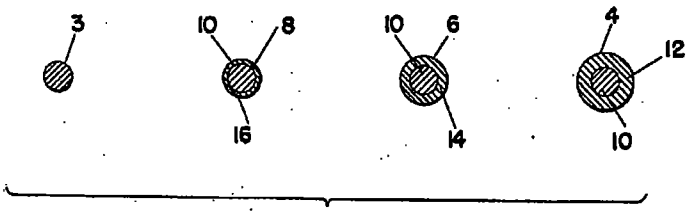


Fig. 2

INVENTOR.
RUDOLPH H. BLYTHE
BY Besser, Smith & Hardy
ATTORNEYS

nited States Patent Office 2,738,303 Patented Mar. 13, 1956

2,738,303

SYMPATHOMIMETIC PREPARATION

Rudolph H. Blythe, Llanerch, Pa., assignor to Smith, Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

Application July 18, 1952, Serial No. 299,566

5 Claims. (Cl. 167—82)

This invention relates to a sympathomimetic preparation and, more particularly, relates to such a preparation providing for timed release of a sympathomimetic agent over a long period of time.

The sympathomimetic agents useful with this invention are organic and inorganic acid addition salts of (racemic) amphetamine, dextro-amphetamine, d-desoxyephedrine and (racemic) desoxyephedrine. Exemplary salts are the hydrochloride, phosphate, sulfate, succinate, tartrate and citrate salts.

In accordance with this invention one of the above sympathomimetic agents, or a combination thereof, is continuously released over a long period of time through the use of a large number of small pellets coated with various thicknesses of a material slowly digestible or dispersible in the gastrointestinal tract.

It has been unexpectedly found that the preparation in accordance with this invention controls the level of sleep throughout the entire period of sleep. By this invention it is practical to accurately control body levels so as to provide a desired level of sleep. The benefits stemming from this result are numerous. Of particular importance, it has been found that the preparation of this invention controls nocturnal seizures associated with epilepsy. Other involuntary reactions occurring during sleep, such as enuresis, are similarly controlled. Again, unexpectedly, the preparation of this invention controls the incidence of migraine headaches occurring on awakening.

Further, when used as an obesity remedy, the constant release of the medicament of this invention over a ten to twelve hour period controls the appetite uniformly throughout the waking hours and hence eliminates one of the greatest factors contributing to obesity, namely, snacking at times other than at regular meal times.

Other beneficial and surprising results have also been noted. Single doses produce jitteriness at peak body levels and subsequently produce mood let-down and irritability on dropping to a low body level. These undesirable side effects have been substantially eliminated. An unexpected increase in the feeling of well being is also achieved.

Again, this invention has surprisingly resulted in a very great increase in reliability, since it has overcome the problem occurring with the single large dosage form heretofore used which frequently became struck en route to the intestines with the resulting delay in medication. Further, the use of a large number of small pellets results in their wide dispersal throughout the intestines.

The dosage unit form in accordance with this invention comprises a capsule containing an initial dose of 2 to 10 mg. of the selected sympathomimetic which is ready for immediate release to the body, being free of any time-delay coating. This 2 to 10 mg. of the selected sympathomimetic can be in the form of numerous uncoated pellets made as described hereafter, or can be simply the crystalline or powdered form of the selected sympathomimetic. This dosage is an amount sufficient to substantially immediately raise the body level to the

optimum effective range. The normal single dosage is larger than the initial dose of this invention in order to achieve long action and results in numerous side effects at peak body levels, particularly jitteriness, subsequent let-down and depression of mood.

In the case of a dextro-amphetamine salt this initial dosage preferably should be from 3 to 5 mg. In the case of a racemic amphetamine salt this initial dosage preferably should be from 5 to 10 mg. In the case of a dextro-desoxyephedrine salt this initial dosage preferably should be from 2 to 5 mg. In the case of a racemic desoxyephedrine salt this initial dosage preferably should be from 4 to 10 mg.

In addition the capsule contains from 50 to about 400, preferably about 100, wax-fat covered pellets of the selected sympathomimetic, each coated pellet containing about the same amount of drug. The wax-fat coatings are selected so as to provide a continuous release of the selected sympathomimetic in an amount to maintain substantially constant the body level established by the uncoated amount of the selected sympathomimetic. These coated pellets will contain a total amount of the selected sympathomimetic of from about 200% to 400% by weight of the uncoated initially released dosage.

Where desired, a sedative, such as, for example, a barbiturate, such as 5-isoamyl-5-ethylbarbituric acid (amobarbital), 5-phenyl-5-ethylbarbituric acid (phenobarbital), 5-ethyl-5-(1-methylbutyl)-barbituric acid (phentobarbital), sodium-5-secbutyl-5-ethyl barbiturate (butabarbital sodium), 5-allyl-5-(1-methylbutyl)-barbituric acid (secobarbital), or N-methyl-5-ethyl-5-phenyl-barbituric acid may be used in admixture with the sympathomimetic agent to form the initially released dosage and in the wax-fat coated pellets. The sedative, when used, should be from about 2 to 8 times the weight of sympathomimetic agent with which it is admixed. The addition of the sedative permits the use of the invention in patients who are very sensitive to sympathomimetics and provides a quieting effect without the depression usually associated with sedatives.

The desired product can be achieved, for example, by combining the uncoated selected sympathomimetic with a plurality of different groups of coated pellets. It is preferred to use 3 groups as a practical matter, but from two to eight groups are satisfactory. It has been found that if the required thickness of coating for release at the end of nine hours is X and the number of coated groups is Y, the first coated group may have a median coating of X/Y, the next group a median coating of 2X/Y, the next 3X/Y, and so on, depending on the number of groups. Following this formula, it has been found that if either of the following techniques are used to make a predetermined median coating for any one group, the coatings will vary within the range of from about 30% to about 40% on either side of the median coating. A satisfactory approximation is achieved where the median coating weights are made up using the above formulae with X representing the weight of the median coating of the group which is released last.

Sympathomimetic pellets in accordance with this invention are readily prepared by utilizing a crystalline or powder form of the selected sympathomimetic and sucrose using procedure well known to the art for making sugar pellets (see, for example, "Confectioner's Journal, January 1951, page 41). By way of more specific example, following the teachings of this publication 20.0 kg. of extended d-amphetamine sulfate is prepared from a mixture of 2.2 kg. of crystalline d-amphetamine sulfate and 17.8 kg. of sucrose. About 200 pellets having a mesh size of from 12–40 are screened out per

each gram. The d-amphetamine sulfate content of the pellets is 10–12% of the total weight.

As is also well known to the art, pellets of the selected sympathomimetic can be readily prepared by placing small sugar pellets (non-pareil seeds) of from about 12 to 40 mesh size in a rotating coating pan and coating them with a powder of the selected sympathomimetic. Before the addition of the powder the sugar pellets are wetted in the conventional manner using, for example, syrup U. S. P., or a gelatin coating solution such as one having the following formula:

	Parts by weight
Sucrose	100
Gelatin	8
Acacia	6
Water	70

If desired, the powdered sympathomimetic can be extended with, for example, calcium sulfate dihydrate, powdered starch or powdered acacia prior to being used in the process. The coating operation is repeated until each pellet contains the desired amount of selected sympathomimetic. After the sympathomimetic pellets have been formed, a number of them are provided with a wax-fat coating which is capable of being slowly disintegrated in the gastro-intestinal tract. Such coatings and their application are all well known to the art, the most common method being to place the desired wax-fat combination in solution and spray it over the pellets during the operation of the coating pan holding the pellets.

The wax-fat coating will preferably be a mixture of glyceryl monostearate and beeswax, the glyceryl monostearate being within the range of from 50 to 95% by weight of the total coating. It is preferred to have the glyceryl monostearate about 90% by weight of the total coating. Any other water-insoluble ingestible wax can be substituted for beeswax. Thus, for example, Japan wax, paraffin, carnauba wax, bayberry wax, and other animal, insect, plant or other water-insoluble, non-toxic, wax-like substances, such as sterols, as, for example, cholesterol, are satisfactory. Any other slowly digestible or dispersible solids, such as slowly digestible fatty esters, slowly dispersible fatty acids and slowly dispersible higher fatty alcohols may be used in place of glyceryl monostearate. Thus, for example, stearic acid, palmitic acid, glyceryl tristearate, cetyl palmitate, diglycol stearate, glyceryl myristate, triethylene glycol monostearate, cetyl alcohol, stearyl alcohol, and the like, are satisfactory. It is preferred to use solid fatty acids and alcohols having from 12 to 22 carbon atoms or esters of said solid fatty acids.

In order to spray the wax-fat coating, the wax-fat constituent can be admixed with a suitable warmed solvent such as carbon tetrachloride heated to about 60° C., the wax-fat solids being within the range of from 5–25% by weight of the solution.

Mixtures of the selected sympathomimetic and sedative can be similarly prepared as pellets and coated.

It will be appreciated that the above described method is merely illustrative of how the product of this invention can be achieved, there being multitudinous other equally satisfactory methods within the scope of the invention.

This invention will be further clarified by reading the following description in conjunction with the drawings, in which:

Figure 1 is a plan view of a capsule containing pellets in accordance with this invention.

Figure 2 is a sectional view of typical pellets contained in the capsule of Figure 1.

As shown in Figure 1 a two piece gelatin capsule 2 contains pellets 3 of a selected sympathomimetic, the pellets being uncoated. Capsule 2 further contains wax-fat coated sympathomimetic pellets 4, 6 and 8. As will be apparent from a study of Figure 1, these various pellets

are in random distribution, there being approximately an equal number of each group or type of pellet.

As shown in Figure 2, each of the pellets 4, 6 and 8 has a center or core 10 of the selected sympathomimetic. The pellets 4 have a wax-fat coating 12 which is of greater thickness than the wax-fat coating 14 of pellets 6, which in turn is of greater thickness than the wax-fat coating 16 of pellets 8. Coatings 12, 14 and 16 shown in Figure 2 represent the median coatings of the groups formed by pellets 4, 6 and 8, it being appreciated that as previously described the coatings of each group of pellets will vary in order to provide gradual release of the selected sympathomimetic over a ten to twelve hour period.

The following examples are illustrative of dosage unit forms in accordance with this invention and their preparation:

Example 1

15.5 kg. of non-pareil seeds (sugar pellets) all passing through a 12 mesh screen, 90% passing through a 40 mesh screen and not over 10% through a 28 mesh screen, were placed in a 36 inch coating pan. The pan was set in rotation and 240 cc. of syrup U. S. P. was added by slowly pouring it on the pellets to evenly wet them. 750 grams of powder, consisting of 80% dextro-amphetamine sulfate and 20% calcium sulfate dihydrate was sprinkled on the wetted mass of non-pareil seeds. The pellets were dried in warm air. The addition of the syrup, dextro-amphetamine sulfate, coating powder and the drying were repeated to apply three additional coats. Talc as a fifth coat was added by wetting the pellets with 240 cc. of syrup and then dusting on 600 gm. of talc. The pellets were rolled until dry and the excess talc was removed by vacuum. 20.0 kg. of dextro-amphetamine sulfate coated pellets were yielded through a 12 mesh screen. One-quarter of the yielded pellets were removed and set aside.

The three-quarters of the batch remaining in the coating pan was coated with a wax-fat coating solution made by admixing 6300 gm. glyceryl monostearate, 700 gm. white beeswax (U. S. P.) and 21,000 cc. of carbon tetrachloride. The wax-fat solution was at a temperature of 70° C. After applying 425 cc. of wax-fat solution, the pellets were dried with air and the coating operation repeated until the weight of the material being coated had increased 10%, at which point one-third of the remaining batch was removed and dusted with talc in a separate coating pan.

The remainder of the batch was further repeatedly coated with the wax-fat solution and dried until the weight of the material increased 10%, over what it weighed when it was separated from the first group of coated pellets, at which time one-half of the remaining pellets were removed and dusted with talc in a separate coating pan.

The remaining pellets were subjected to further repeated coating with the wax-fat solution and drying until the weight of this group of pellets had increased about 10% over the weight of the group from which it had been separated immediately previously. These pellets were then dusted with talc. The weight of the coating of each group was found to vary about ±35% of the median weight of coating of the group involved.

The four groups of pellets thus formed were all placed in a single container and thoroughly mixed to provide a uniform mixture.

Size No. 3 gelatin capsules were then filled with the thus mixed pellets to provide a total dosage of 15 mgs. of dextro-amphetamine sulfate per capsule. Each capsule contained about 100 pellets.

Each No. 3 capsule provided the desired body level of dextro-amphetamine sulfate in about one-half hour. The coated groups provided a continuous release of dextro-amphetamine sulfate and maintained this desired body level for approximately eleven hours.

Example 2

The steps of Example 1 were repeated with the exception that d-desoxyephedrine hydrochloride was substituted for dextro-amphetamine sulfate.

Example 3

The steps of Example 1 were repeated with the exception that racemic amphetamine phosphate was substituted for dextroamphetamine sulfate and No. 1 gelatin capsules used.

Example 4

The steps of Example 1 were repeated with the exception that racemic desoxyephedrine citrate was substituted for dextroamphetamine sulfate and No. 2 gelatin capsules used.

Example 5

4 kg. of non-pareil seeds (sugar pellets), all passing through a 20 mesh screen, were placed in a 24 inch coating pan. The pan was set in rotation and 120 cc. of gelatin coating solution, having the formula set out in column 3 herein, at 60° C. was slowly added to the pellets in such a manner as to evenly wet the sugar seeds. 200 grams of "Dexamyl" coating powder, having the following composition, was scattered over the wetted mass of sugar pellets:

	Grams
Amobarbital (5-isoamyl-5-ethylbarbituric acid)	3250.0
d-Amphetamine sulfate	500.0
(Passed through #80 mesh screen)	

The pellets were then dried using warm air. The addition of the warm gelatin coating solution, amobarbital-dextro-amphetamine sulfate coating powder was repeated 18 times. The pellets were dried with warm air and loose powder in pan was sucked out with a vacuum. The product was freed of lumps by passing through a #14 screen and ⅛ of the yield was set aside.

The two-thirds of the batch remaining in the coating pan was coated with a wax-fat coating solution, made by admixing 1800 grams of glyceryl monostearate, 200 grams of white beeswax (U. S. P.), and 6,000 cc. of carbon tetrachloride. The wax-fat solution was at a temperature of 70° C. After applying 300 cc. of wax-fat solution, the pellets were dried with air and the coating operations repeated until the weight of the material being coated had increased 12.5%. At this point, one-half of the wax-fat coated pellets were removed from the pan and set aside to dry overnight.

The remaining pellets in the coating pan were subjected to further repeated coating, using the warm wax-fat solution until the batch of the material being coated had increased an additional 12.5% in weight. The coated pellets were then dried overnight.

The three groups of pellets thus formed were all placed in a single container and thoroughly mixed to provide a uniform mixture.

No. 1 gelatin capsules were then filled with the thus mixed pellets to provide a total dosage of 97.5 mg. of amobarbital and 15 mg. of dextro-amphetamine sulfate. Each capsule contained about 350 pellets.

Each #1 capsule provided the desired body level of amobarbital and dextro-amphetamine sulfate in about 45 minutes. The coated groups provided a continuous release of amobarbital and dextro-amphetamine sulfate and maintained this desired body level for approximately 12 hours.

It is not desired to be limited except as set forth in the following claims, the above description being by way of illustration only.

What is claimed is:

1. A therapeutic preparation in dosage unit form comprising a capsule containing an initial dosage of from 2 to 10 mg. of sympathomimetic selected from the group consisting of a salt of racemic amphetamine, a salt of dextro-amphetamine, a salt of racemic desoxyephedrine and a salt of dextro-desoxyephedrine to provide a predetermined body level of the selected sympathomimetic, a minimum of 50 pellets containing the selected sympathomimetic in an amount of about 200 to 400% by weight of said initial dosage and having ingestible coatings resistant to disintegration in the gastro-intestinal tract, the coatings being of varying thicknesses to provide for the gradual release of the selected sympathomimetic, said preparation maintaining a substantially constant body level of the selected sympathomimetic over a period of about ten to twelve hours.

2. A therapeutic preparation in dosage unit form comprising a capsule containing an initial dosage of from 2 to 10 mg. of a sympathomimetic selected from the group consisting of a salt of racemic amphetamine, a salt of dextro-amphetamine, a salt of racemic desoxyephedrine and a salt of dextro-desoxyephedrine to provide a predetermined body level of the selected sympathomimetic, 50 to about 400 pellets containing the selected sympathomimetic in an amount of about 200 to 400% by weight of said initial dosage and having ingestible wax-fat coatings resistant to disintegration in the gastro-intestinal tract, the coatings being of varying thicknesses to provide for the gradual release of the selected sympathomimetic, said preparation maintaining a substantially constant body level of the selected sympathomimetic over a period of about ten to twelve hours.

3. A therapeutic preparation in dosage unit form comprising a capsule containing an initial dosage of from 2 to 10 mg. of a sympathomimetic selected from the group consisting of a salt of racemic amphetamine, a salt of dextro-amphetamine, a salt of racemic desoxyephedrine, and a salt of dextro-desoxyephedrine and a sedative to provide a predetermined body level of the selected sympathomimetic, 50 to about 400 pellets containing the selected sympathomimetic in an amount of about 200 to 400% by weight of said initial dosage and a sedative and having ingestible wax-fat coatings resistant to disintegration in the gastro-intestinal tract, the coatings being of varying thicknesses to provide for the gradual release of the selected sympathomimetic, said preparation maintaining a substantially constant body level of the selected sympathomimetic over a period of about ten to twelve hours.

4. A therapeutic preparation in dosage unit form comprising a capsule containing an initial dosage of from 2 to 10 mg. of sympathomimetic selected from the group consisting of a salt of racemic amphetamine, a salt of dextro-amphetamine, a salt of racemic desoxyephedrine and a salt of dextro-desoxyephedrine to provide a predetermined body level of the selected sympathomimetic, a minimum of 50 pellets containing the selected sympathomimetic in an amount of about 200 to 400% by weight of said initial dosage and having ingestible coatings resistant to disintegration in the gastro-intestinal tract, the coatings being of varying thicknesses to provide for the gradual release of the selected sympathomimetic, each of said pellets having a substantially spherical core containing the selected sympathomimetic, and said preparation maintaining a substantially constant body level of the selected sympathomimetic over a period of about ten to twelve hours.

5. A therapeutic preparation in dosage unit form comprising a capsule containing an initial dosage of from 2 to 10 mg. of sympathomimetic selected from the group consisting of a salt of racemic amphetamine, a salt of dextro-amphetamine, a salt of racemic desoxyephedrine and a salt of dextro-desoxyephedrine to provide a predetermined body level of the selected sympathomimetic, a minimum of 50 pellets containing the selected sympathomimetic in an amount of about 200 to 400% by weight of said initial dosage and having ingestible coatings resistant to disintegration in the gastro-intestinal tract, the coatings being of varying thicknesses to provide for the gradual release of the selected sympathomimetic, each of said

pellets having a substantially spherical core containing the selected sympathomimetic with the medicament overlying a substantially spherical innocuous seed, and said preparation maintaining a substantially constant body level of the selected sympathomimetic over a period of about ten to twelve hours.

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EXHIBIT 4

ENTIRE EXHIBIT UNDER SEAL

EXHIBIT 5

ENTIRE EXHIBIT UNDER SEAL

CERTIFICATE OF SERVICE

I hereby certify that on the 30th day of May 2007 I electronically filed the foregoing document, **REDACTED VERSION OF DECLARATION OF ARTHUR H. KIBBE, Ph.D. IN SUPPORT OF DEFENDANT'S RESPONSIVE CLAIM CONSTRUCTION BRIEF,** with the Clerk of the Court using CM/ECF which sent notification of such filing to the following:

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